Our road to growth

The infectious disease arena and, in particular, infectious disease vaccines offer major opportunities for companies such as Acambis. Through factors such as an increased emphasis on preventative medicine in Western countries, emergence of new diseases, continued growth in travel to endemic regions and concerns about the threat of viruses and bacteria being used as biological weapons, vaccines are now recognised internationally as a critical part of health management strategies. Vaccines, which are Acambis' focus, continue to represent the fastest-growing ID sector, with a compound annual growth rate of almost 26% between 1999 and 2003.[1]

Acambis aims to become a fully integrated biopharmaceutical company, targeting infectious diseases. We have identified four key components to deliver that goal:

Exploit our smallpox franchise to the full

Drive the development of new products

Develop and leverage core capabilities

Improve the predictability of our revenue stream

SMALLPOX FRANCHISE

Much of our recent success has come from government contracts for our new, investigational smallpox vaccine. Governments and other bodies are keen to ensure that they are prepared for potential smallpox outbreaks. Acambis is at the forefront of helping governments to meet that need.

We have positioned ourselves to gain maximum benefit from the smallpox biodefence opportunity, which offers the possibility for both profitable, short-term revenues from government stockpiling contracts and sustainable revenues from ongoing 'warm-base' manufacturing and stockpile maintenance.

PRODUCT PIPELINE

A clear benefit to Acambis of the smallpox franchise is that it generates cash for us to invest in the product development pipeline, which is the main driver of medium- to long-term value and growth. We maintain a balanced pipeline of early-, mid- and late-stage programmes to maximise our probability of success. The products we have in development reflect key areas of expansion within the vaccine industry, including biodefence, travel, emerging diseases and those individuals, such as the elderly, whose weaker immune systems put them at greater risk of suffering severe effects from an infection.

CORE CAPABILITIES

We are continuing to build our core capabilities. We have built significant clinical development and regulatory expertise, plus manufacturing capacity and the requisite QA/QC expertise to oversee product development and manufacture. We also have a US travel vaccines sales, marketing and distribution infrastructure.

These core capabilities, together with our balance sheet strength, enable us to increase the retained value of our product pipeline by investing in and conducting product development ourselves and, wherever possible, manufacturing products in-house and marketing them. Where we are able to use our own resources we can gain greater control over our operations and also retain a greater proportion of a product's profit margin than if we out-licensed it to a pharmaceutical company, contracted third-party manufacture or used a distributor to market and/or sell it.

REVENUE STREAM

Whilst bidding for government contracts remains a major part of our business, our revenues will continue to be volatile and unpredictable. Clearly, we want to maximise those revenue streams, but we also want to develop predictable revenues from sustainable business. As our existing pipeline is not expected to make a substantial contribution to revenues before 2008, at the earliest, we are seeking to leverage our strengths to bring in additional projects and revenues through in-licensing, partnering or acquisition.

Acambis' strategy is overseen and approved by our Board of Directors. From left to right, they are:
Ross Graham, Non-executive Director
Dr Thomas Monath, Chief Scientific Officer
Elizabeth Brown, Company Secretary
Alan Smith, Chairman
Gordon Cameron OBE, Chief Executive Officer
Michael Lytton, Non-executive Director
David Lawrence, Chief Financial Officer
Dr Randal Chase, Non-executive Director
Alan Dalby, Non-executive Director

About our industry

There are an estimated 200 companies operating in the vaccine arena[1], the majority developing around 600 products. The five major players – SP, GSK, Merck, Wyeth and Chiron – generated around 83% of the $8.9bn annual worldwide sales[2] in 2003, with other sales being shared between mid-size companies such as Acambis, Baxter, Vaccines, Berna Biotech, ID Biomedical and Solvay.

Typically, these mid-size companies, like Acambis, employ between 250 and 1,000 employees, are entrepreneurial in development, their infrastructures, including manufacturing and marketing, and tend to have varied geographical coverage. They may sell some products and have late-stage development programmes but may not be inclined to outlicense products except for gaps in expertise or coverage that they lack.

The need for long-term investment in R&D, considerable manufacturing capacity and capability, and the ever-increasing regulatory burden, have established high barriers to entry and encouraged industry consolidation to bring the required access to products, expertise or expanded geographical reach. Recent examples include ID Biomedical's acquisition of Shire's vaccine business, Chiron's acquisition of Powderject and Berna Biotech's acquisition of Rhein Biotech.

Although the majority of sales today are for paediatric vaccines, elective vaccination of adolescents, adults and the elderly is gaining profile. Target markets include new vaccines for diseases associated with pregnancy, sexual contact, overseas travel, hospital-acquired infections, as well as the more well-known travel, military, vaccination markets, biodefence vaccines and the high profile influenza market.

1 Datamonitor, 'Commercial Insight: Vaccines', July 2004
2 Ibid.

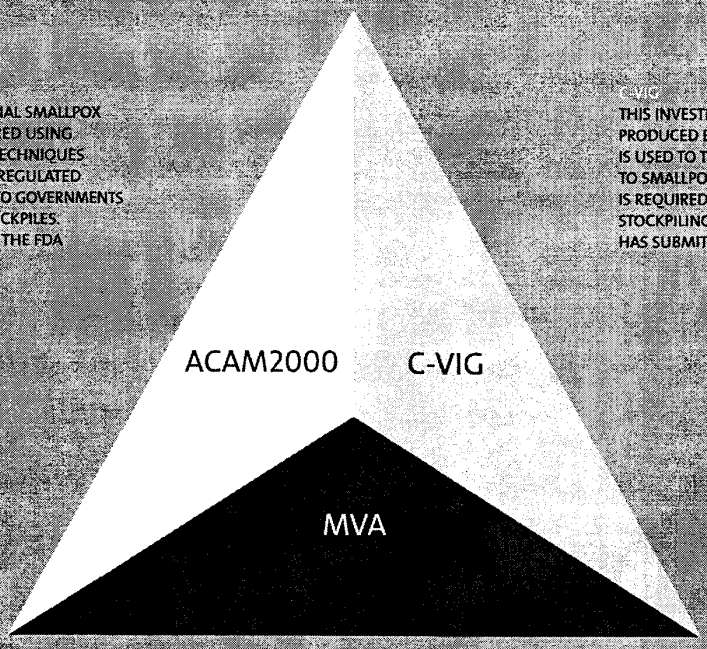
Exploiting the smallpox franchise to the full

We are one of only a handful of companies competing in the smallpox vaccine arena and, through the number of contracts we have won and the extent of clinical development work we have undertaken, have positioned ourselves at the forefront of this market.

Our franchise is built around three programmes:

ACAM2000
THIS NEW, INVESTIGATIONAL SMALLPOX VACCINE IS MANUFACTURED USING MODERN CELL-CULTURE TECHNIQUES TO TODAY'S RIGOROUSLY REGULATED STANDARDS AND IS SOLD TO GOVERNMENTS FOR EMERGENCY-USE STOCKPILES. SUBMISSION OF A BLA TO THE FDA IS PLANNED IN 2005.

C-VIG
THIS INVESTIGATIONAL PRODUCT, PRODUCED BY CANGENE CORPORATION, IS USED TO TREAT ADVERSE REACTIONS TO SMALLPOX VACCINATION AND, AS SUCH, IS REQUIRED BY ANY GOVERNMENT STOCKPILING SMALLPOX VACCINE. CANGENE HAS SUBMITTED A BLA TO THE FDA.



MVA
THIS INVESTIGATIONAL WEAKENED SMALLPOX VACCINE MAY BE SUITABLE FOR PEOPLE FOR WHOM MAINSTREAM SMALLPOX VACCINES ARE CONTRAINDICATED, SUCH AS THOSE WITH DISORDERS OF THE IMMUNE SYSTEM OR SKIN CONDITIONS SUCH AS ECZEMA. CLINICAL TESTING OF THIS VACCINE IS ONGOING.

Our smallpox franchise is important to us for two reasons: first, further stockpiling contracts with the US or other governments for our ACAM2000 and MVA smallpox vaccines could generate significant revenues; and, second, we aim to fulfil the US Government's requirement for ongoing manufacturing capabilities, which could generate longer-term, predictable revenues.

ACAM2000 – US GOVERNMENT REQUIREMENTS

The US Government has established an emergency-use stockpile containing 182.5 million doses of investigational ACAM2000. In addition, it has an estimated 10-15 million doses of Wyeth's Dryvax® and 85 million doses of SP's 'Wetvax', both of which were manufactured using traditional methods that are no longer acceptable. With these doses, the US believes that it has a stockpile sufficient to meet its vaccination needs if there were a smallpox outbreak.

We aim to place our current relationship with the US Government on a more long-term footing through fulfilling its requirement for an ongoing smallpox vaccine manufacturing capability, known as 'warm-base' manufacturing. The systems and procedures we established under our current US Government contracts are a major asset to the US in its ongoing biodefence plans. Through warm-base manufacturing, annual production runs would test our systems and procedures to ensure that we could rapidly ramp up production, if required by the US. Such arrangements are already typical for defence contractors.

Vaccine doses produced through warm-base manufacturing would continue to supply the US's stockpile, potentially replacing the old vaccine and any doses of ACAM2000 that, over time, fall below accepted potency levels. In addition, although warm-base manufacturing would set a base-line annual production level, it would also give the US Government a flexible ordering mechanism by which it could increase the level of production in any given year if a higher number of doses were required for maintenance or replenishment of the stockpile. One of our key goals is to secure a warm-base manufacturing contract during 2005.

MVA – US GOVERNMENT PROCUREMENT

The US has also indicated its intention to procure a stockpile of an attenuated smallpox vaccine, such as MVA, for the proportion of the population for whom the traditional smallpox vaccine is contraindicated. Congressional Budget Office estimates for the Project Bioshield Act,[2] which was passed by US Congress in July 2004, indicate that procuring such a stockpile could cost up to an estimated $900m. The US Government is widely expected to conduct a tender process during 2005 to award a contract or contracts to supply the stockpile.

Winning some or all of a US Government contract could bring sufficient revenues to contribute to bridging the gap between the major revenues of our US Government ACAM2000 contract, being recognised between 2002 and 2006, and the potential future revenues from our R&D pipeline from about 2008. It would also generate additional cash to invest in product development and other opportunities.

As one of two companies awarded US Government MVA development and manufacturing contracts in February 2003 and September 2004, we are extremely well positioned to bid for the stockpile contract. Our partnership on this project with Baxter combines its extensive manufacturing capacity and knowledge with our considerable expertise in government contracting, clinical development and regulatory affairs, developed through our previous US Government contracts. The Acambis/Baxter partnership has a strong track-record established through our work on the ACAM2000 US Government contract.

ACAM2000 – OTHER GOVERNMENT CONTRACTS

The US has, undoubtedly, taken the lead in establishing smallpox vaccine stockpiles, but many other governments continue to issue procurement contracts for mainstream vaccine, such as ACAM2000. Baxter markets ACAM2000 and C-VIG on our behalf outside the US and the UK.[1] We are competing, principally, with SP and Bavarian Nordic, both of whom have previously supplied doses of investigational, cell culture-derived smallpox vaccine to governments. However, there is no widely available, licensed vaccine and we believe that the extensive clinical trial data package we have generated on ACAM2000 already gives us a major competitive advantage in discussions with governments, which would be increased with licensure. We plan to submit a BLA to the FDA in 2005.

In the last two years, in conjunction with Baxter, we have won contracts of varying size with 13 governments, the majority being in Europe. Although no country has issued a contract as sizeable as the US's nor is currently expected to do so, we ensure we are positioned to maximise every opportunity that exists.

1 Acambis is sales agent for C-VIG outside North America and Israel and Baxter assists us in marketing C-VIG
2 Congressional Budget Office estimate, May 2003

Driving the product pipeline forward

Our product pipeline is critical to the future success of Acambis. We aim to develop a balance of short-, medium- and long-term projects that, ultimately, will enable us to generate a regular and sustained flow of new products coming to market.

In January 2004, we completed a strategic review of our R&D pipeline and selected seven clinical-stage programmes to pursue. These were chosen based on a combination of their technical probability of success and the potential commercial opportunity. By focusing our resources on these programmes, we aim to drive these vaccines through to licensure as rapidly as possible. We will also continue to review opportunities to supplement our pipeline.

Our portfolio includes one licensed product and seven vaccines in development, plus several more at earlier stages.

The licensed product we sell is an oral typhoid vaccine, Vivotif®, which is owned and manufactured by Berna Biotech. We have North American sales rights through our BPC sales, marketing and distribution company, which principally sells to travel clinics and has also previously handled military contracts.

ACAM2000 and MVA are both investigational smallpox vaccines and are intended for government emergency-use stockpiling. Sales of ACAM2000 to governments for emergency-use stockpiles are currently made under an FDA IND application. Further information on these and a related product, C-VIG, for which we are sales agent, is provided on pages 6 and 7.

We have the opportunity to channel two of the vaccines we currently have in development through BPC for both the US travel vaccine and military markets. ARILVAX™ is a yellow fever vaccine owned and manufactured by Chiron Vaccines for which we have US sales rights. ChimeriVax-JE, which we developed using our proprietary ChimeriVax™ technology, targets the mosquito-borne JE virus.

In addition to the travel vaccine market, there is likely to be a more significant market opportunity for

ACAMBIS' PORTFOLIO		PHASE I	PHASE II
ACAM2000	SMALLPOX VACCINE CURRENTLY SOLD UNDER FDA IND TO GOVERNMENTS FOR EMERGENCY-USE STOCKPILES		
MVA	WEAKENED SMALLPOX VACCINE BEING DEVELOPED FOR IMMUNOCOMPROMISED		
C-VIG	TREATMENT FOR REACTIONS TO SMALLPOX VACCINATION. SALES AGENT TO CANGENE OUTSIDE N. AMERICA AND ISRAEL		
VIVOTIF®	N. AMERICAN SALES RIGHTS FROM BERNA BIOTECH TO LICENSED PROPHYLACTIC ORAL TYPHOID VACCINE		
ARILVAX™	US SALES RIGHTS TO CHIRON'S YELLOW FEVER VACCINE		
CHIMERIVAX-JE	VACCINE AGAINST VIRAL DISEASE, JAPANESE ENCEPHALITIS, FOR ENDEMIC AND TRAVEL MARKETS		
CHIMERIVAX-WEST NILE	VACCINE AGAINST WEST NILE VIRUS, PRIMARILY FOR N. AMERICAN MARKET		
CHIMERIVAX-DENGUE	VACCINE AGAINST DENGUE FEVER LICENSED TO SP		
C. DIFFICILE	TO TREAT OR PREVENT C.DIFFICILE-ASSOCIATED DIARRHOEA, A HOSPITAL-ACQUIRED BACTERIAL INFECTION		

*The above table represents Acambis' current internal best estimates of the earliest possible dates of when products may be licensed. As ever, these are subject to risks and uncertainties that may cause actual results to differ materially from those projected.

ChimeriVax-JE in the regions of the world where the virus is endemic, such as south and east Asia, and north Australia. We have retained full rights to this programme, including manufacturing, which takes place at our Canton, MA facility, and have the ability to conduct clinical development ourselves in countries such as the US, but may look for endemic region partners to facilitate development/licensure and sales, marketing and distribution.

West Nile is a high-profile example of the impact of emerging infectious diseases. It had never been seen in the US before 1999 but, since then, it has spread throughout the country causing disease in more than 16,000 people and over 650 deaths. Infection with this mosquito-borne virus is of greatest threat to those aged 50 and above, who would be the primary target for a vaccine. Our market for vaccine sales would, therefore, be Primary Care Physicians, which requires an extensive distribution infrastructure beyond our current capabilities. Using our core capabilities, we plan to conduct clinical development and manufacture ourselves and look for a marketing or distribution partner when closer to licensure.

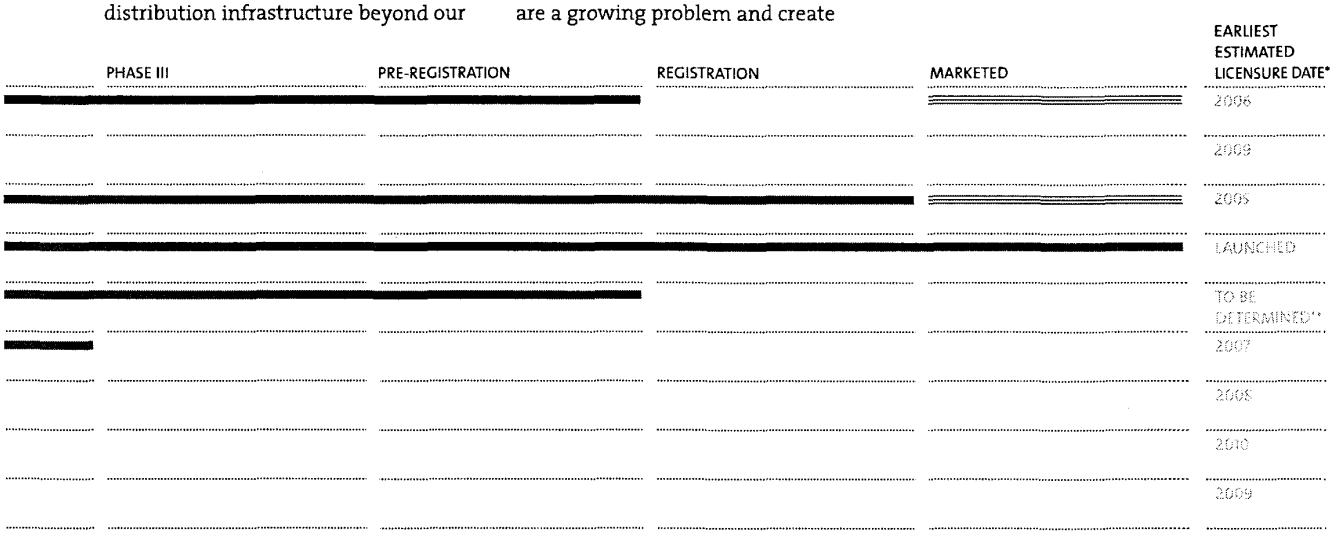
With an estimated 50 million cases of dengue virus-related illness a year, ChimeriVax-Dengue could be the single largest market opportunity in our pipeline. Worldwide rights are licensed to SP. It fully funds the development programme and has responsibility for manufacturing and further clinical development. Acambis is entitled to milestone payments and a royalty on any sales.

Our *C. difficile* vaccine is the one therapeutic vaccine we currently have in development and is intended, initially, to be a treatment for those suffering from *C. difficile*-associated diarrhoea, which is generally acquired in institutional settings, such as hospitals or nursing homes. Such hospital-acquired infections are a growing problem and create a significant burden for healthcare systems. As with ChimeriVax-West Nile, we would require a partner with specialised marketing/distribution capability for *C. difficile*.

PIPELINE PROGRESS

In 2005, we aim to progress several of our key development programmes into their next stage. This includes filing a product licence application for ACAM2000, initiating a pivotal Phase III trial of ChimeriVax-JE, progressing MVA, ChimeriVax-West Nile and ChimeriVax-Dengue into the next stage and undertaking Phase I trials of our *C. difficile* vaccine.

We also have a number of earlier-stage projects that we aim to progress closer to clinical development during 2005.



**For an update on ARILVAX, refer to our Operating Review on page 21